BDCM Comments to DART IC

Presented by

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Data Summary

- Epidemiology:
  - 9 studies looked at 8 reproductive / developmental measures
  - 6 of 8 measures = no associations
  - 1 measure (spontaneous abortion) shown to be a false positive by a far more robust negative study
  - 1 measure (neural tube defect) was equivocal (one + / one -)
- Toxicology:
  - State of the art study = no developmental toxicity
  - State of the art 2-generation study = no reproductive toxicity
  - 3 Hypothesis-generating studies under physiologically unrealistic circumstances are not relevant to humans exposed to BDCM in chlorinated water

Overall Conclusion

- Epidemiology and toxicology studies indicate that BDCM has not been clearly shown to be a reproductive toxicant in humans or laboratory animals

Approach

- Review and evaluate relevant and available epidemiology and toxicology data

- Major data sources:
  - Review by Graves *et al*., 2001
  - Review by Tardiff *et al*., 2006
  - An additional epidemiology study: Nieuwenhuijsen *et al*., 2007
  - An additional toxicology study: Bielmeier *et al*., 2007

Epidemiology Findings Related to BDCM

- **Oral cleft**: 1 study, no association
  [Dodds & King, 2001]
- **Cardiac defects**: 1 study,
  no association [Dodds & King, 2001]
- **Chromosomal abnormalities**:
  1 study, no association
  [Dodds & King, 2001]
- **Stillbirth**: 1 study, no association
  [Dodds *et al*., 2004]
- **Intra-uterine growth retardation**:
  3 studies, no association [Infante-Rivard, 2004; Hinkley *et al*., 2005; Porter *et al*., 2005]

Epidemiology Findings Related to BDCM (cont)

- **Small for gestational age**: 1 study, no association [Wright *et al*., 2004]
- **Preterm delivery**: 2 studies, no association [Wright *et al*., 2004; Savitz *et al*., 2005]
- **Neural tube defects**: 2 studies, results equivocal [(+) Dodds & King, 2001; (-) Klotz & Pyrch, 1998]
- **Spontaneous abortion**: 2 studies, one association [Waller *et al*., 1998] followed by another of far more robust design with no association [Savitz *et al*., 2005]

Conclusion

- Epidemiology studies indicate that BDCM has not been clearly shown to be a reproductive toxicant in humans

Reproductive Toxicity Study (Christian *et al*., 2002)

- Two-generation contemporary design for BDCM continuously in tap water (30 P/dose group)
- Doses to 📖 SD rats = 0, 50 150, 450, and 900 mg/L [= 0 to 109 mg/kg-day]
- No abnormalities observed in F1 & F2
- Statistically significant effects at 2 top doses of P & F1: Mortality & clinical signs associated with reduced absolute and relative water intake, reduced body weights & gains, & reduced feed consumption, delayed sexual maturation
- No toxicity in F2 generation
- NOAEL for F1 = at least 50 mg/L
  (≈ 4.1 – 12.6 mg/kg-day or 5,125 – 15,750 times human adult exposure)

Developmental Toxicity Study (Christian *et al*., 2001)

- One-generation contemporary design for BDCM in tap water (25/dose group)
- Doses:
  - 🕮 SD rats = 0, 50 150, 450, and 900 mg/L [= 0 to 82 mg/kg-day]
  - 🕮 SPF rabbits = 0, 15, 150, 450, and 900 mg/L [= 0 to 55 mg/kg-day]
- Maternal pathology in rats & rabbits:
  - Reduced abs. & rel. H2O consumption (↜ 50 ppm)
  - Reduced body weight gain (↜ 450 ppm)
  - Reduced relative food consumption (↜ 450 ppm)
- Additional maternal pathology in rabbits:
  - Weight loss (900 ppm)
- No skeletal changes & no changes in embryo-fetal viability

Developmental Toxicity Study (Christian *et al*., 2001)

- Pathology in Rat Fetuses
  - Minimal delay in ossification of forepaws & phalanges & hindpaws & metatarsals (900 ppm); effects were marginal, reversible, & associated with severely reduced maternal weight gain
- NOAEL, Maternal:
  - Rat = 18.4 mg/kg-day (150 ppm)
  - Rabbit = 13.4 mg/kg-day (150 ppm)
- NOAEL, Developmental:
  - **Rat = 45 mg/kg-day (450 ppm)**
  - Rabbit = 55.3 mg/kg-day (900 ppm)
- Margin of Exposure: ≈ 56,000 to 70,000 between developmental NOAEL (rat, rabbit) and human doses [≈ 0.0008 mg/kg-day]

Data Summary

- Epidemiology:
  - 9 studies looked at 8 reproductive / developmental measures
  - 6 of 8 measures = no associations
  - 1 measure (SAB) showed to be a false positive by a far more robust negative study
  - 1 measure (NTD) was equivocal (one + / one -)
- Toxicology:
  - State of the art study = no developmental toxicity
  - State of the art 2-generation study = no reproductive toxicity
  - 3 Hypothesis-generating studies at physiologically unrealistic circumstances are not relevant to humans exposed to BDCM in chlorinated water

Overall Conclusion

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Regulatory Consideration

- Proposition 65 exempts drinking water:
  See Sections 12502 and 25249.11 of Statute

Q & A

- Thank you